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Is CT-P13 As Effective As Infliximab In Controlling Pain In Adult Patients With Rheumatoid Arthritis?

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Is CT-P13 As Effective As Infliximab In Controlling Pain In Adult Patients With Rheumatoid Arthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not CT-P13 is as good as infliximab in controlling pain in adult patients with rheumatoid arthritis.

STUDY DESIGN: A review of three double-blind randomized controlled trials that were published in English after 2008 were used.

DATA SOURCES: Data sources include peer reviewed articles that were published on PubMed database. They were selected based on their relevance to the research question as well as patient measured outcomes.

OUTCOMES MEASURED: The outcomes measured include efficacy of the drug measured through Visual Analog Scale (VAS), pain on DAS28 scale and pain on the ACR20 scale.

RESULTS: All three studies found that CT-P13 was as effective in reducing pain when compared to infliximab in treating rheumatoid arthritis. One study found that the mean change from baseline using the VAS +/- SD was -30.2 +/- 28 for CT-P13 and was -28 +/- 26.9 for infliximab with a 95% CI (Yoo DH, Racewicz A, Brzezicki J, et al. Arthritis Res Ther. 2016;18. doi: 10.1186/s13075-016-0981-6). Another study compared the change in the DAS28 score and saw the mean decrease from baseline of 2.2 with infliximab and 2.1 with CT-P13 with a CI of 95% (Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, Lundin KE, Mørk C, Jahnsen J, Kvien TK, *Lancet*. 2017;389(10086):2304-2316 doi: 10.1016/S0140-6736(17)30068-5). In Yoo, Prodanovic, Jaworski J, et al. the mean change in VAS from week 54 to week 102 for the maintenance group and switch group was -1.1 and -2.6 (Ann Rheum Di. 2017;76(2):355-363. doi: 10.1136/annrheumdis-2015-208786).

CONCLUSION: Two studies were able to statistically show that CT-P13 was able to improve pain as well as infliximab and one study results were inconclusive as to whether CT-P13 was as effective as infliximab in controlling pain in patients with RA

KEY WORDS: Infliximab, biosimilar, anti-inflammatory disease

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. It effects the lining of the joints, starting in small joints and spreading to larger ones. Over time, it can lead to erosion of the bone and cause irreversible joint deformities. The disease can wax and wane in severity from patients having a flare to being in relative remission.[1] RA can have a systemic effect on the body damaging things such as the blood vessels, heart, lungs, kidneys, eyes, nerves, and skin.[1] It affects about 1% of the population and affects women more than men in a 3:1 ratio.[2]

The specific cause of RA is unknown, however, the incidence and severity of RA has been linked with multiple genes including HLA DRB1 being the best genetic risk factor.[3] Along with genetic components, there are some environmental factors, such as cigarette smoking, connected to an RA diagnosis.[4] Rheumatoid arthritis can range in severity making it hard to find an exact number of healthcare visits patients utilize yearly. A report from 2013 states there were over 105.7 million healthcare visits for arthritis and other rheumatic conditions (AORC).[5] That same study shows that RA is the 3rd most common cause for hospitalization for people with AORC.[5] An exact number for the total healthcare cost of rheumatoid arthritis has not been calculated since 2005, but at that time the annual cost for the disease was $39.2 billion.[6]

RA is generally managed by rheumatologists, but because the disease can present as a systemic disease, it can be seen and managed by many practitioners in the medical field.[2] Since RA is a progressive disease it is normally treated in a stepwise fashion. It is initially treated with disease modifying antirheumatic drugs (DMARDs).[3] During flares or while the patient is waiting for the DMARD to take effect, a low dose corticosteroids can be used to reduce inflammation.[3] NSAIDs can be used to treat pain alongside DMARDs, but cannot be used as monotherapy.[3]

Biologics such as infliximab can be used alone or in combination with oral DMARDs for patients who have failed initial DMARD therapy.[3]

Infliximab and other biologics have been used for many years to treat diseases such as RA. Due to increasing prices of medicine and the recent expiration of the infliximab patent, new biosimilars like CT-P13 are being proposed to treat RA the same way as infliximab but at a lower cost.[7] A 100mg vial of reconstituted Infliximab cost $1,401.38 and a 100mg vial of reconstituted CT-P13 is $1,135.54.[8] The patient will use multiple vials per treatment and will need treatments at 0, 2, 6 weeks and every 8 weeks after that.[8] If a patient uses CT-P13 it can save the patient thousands of dollars over the span of the disease relieving some of the burden of healthcare costs.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not CT-P13 is as good as infliximab in controlling pain in adult patients with rheumatoid arthritis.

METHODS

The articles were published after 2008 and in English. They were narrowed down using keywords such as “Infliximab,” “biosimilar,” and “anti-inflammatory disease.” The articles were then chosen based on their relevance to the clinical question and whether their outcomes were patient oriented evidence that matters (POEMS). Inclusion and exclusion criteria were used while searching for these articles. To help identify relevant articles, the following inclusion criteria was used: RCTs, published in 2008 and later, human subjects, CT-P13, infliximab, and inflammatory disease. Exclusion criteria were other biosimilars, other languages, and anything published before 2008. Table 1 displays the inclusion and exclusion criteria used in each study.

Values reported in the studies that were relevant to the clinical question were the confidence interval (CI), mean change from baseline, and standard deviation and change from baseline.

Three double blind randomized control trials (RCT) articles were used for this EBM review. They focused on adults with rheumatoid arthritis between 18-75 years old. The intervention being observed in each study was CT-P13 treatment and the comparisons were patients being given infliximab or switching patients from infliximab to CT-P13. The outcome measured in these studies was pain reduction using the visual analog scale (VAS), the DAS28 scale, and the ACR20.

TABLE 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Yoo, 2016[6]	RCT	606	18-75	Pts with RA ≥1 year, active disease that did not respond adequately to MTX for ≥ 3 months	Pts who did not have active diseases, not in age range ,or responded to MTX.	151	2hr IV infusion of CT-P13 or infliximab at week 0, 2, & 6, then every 8 weeks until 54 weeks
Jørgensen 2017[9]	RCT	482	18-75	A clinical diagnosis of either rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, crohn's disease or chronic plaque psoriasis, Male or non-pregnant, non-nursing female, >18 y/o at screening, Stable treatment of innovator infliximab during the last 6 months, Subject capable of	Major co-morbidities, such as severe malignancies, severe DM, severe infxs, uncontrollable HTN, severe CVD, severe respiratory diseases and/or other diseases including inflam conditions for which infliximab is contraindicated. Change of major co-medication during the last 2mo prior to randomization: Inadequate birth control, pregnancy, and/or breastfeeding. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible Change in treatment with innovator infliximab during the last 6 months due to disease related	73	Pt were randomized & received infliximab or CT-P13 infusions on set schedule

				understanding and signing an informed consent form Provision of written informed consent	factors, not including dose/frequency adjustments due to drug concentration measurements For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ		
Yoo, 2017[10]	RCT	302	18-75	Completed original PLANTERA study	Not signing new informed consent, pts from institutions that did not approve the study	41	6 infusions of CT-P13 between weeks 62-102

OUTCOMES MEASURED

Outcomes were measured using VAS, DAS28 scores, and ACR20 scores. The VAS scale allowed the patients to rate their pain on a scale of 0 (being no pain) and 100 (being worst pain imaginable). In Yoo DH, Racewicz A, Brzezicki J, et al mean change in VAS outcomes were measured at baseline, week 14, week 30 and week 54[6] and in Yoo DH, Prodanovic N, Jaworski J, et al they were measured at week 54 and week 102.[10] Each new measurement from the scale was compared to the patient's baseline to see if there was any difference in improvement between the treatments. The DAS28 score measures the disease activity state of 28 joints. The score is calculated by counting the number of swollen joints, counting the number of tender joints, taking blood to measure the ESR or CRP, and asking the patient to make a 'global assessment of healthcare.[11] The DAS28 scale was measured at baseline and at 52 weeks and included the change from baseline. [9] The American College of Rheumatology 20 (ACR20) is measured as a 20% improvement in the number of tender and swollen joints, and a 20% improvement in three of the five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein.[12]

RESULTS

Three double blind randomized control trials were assessed to see if CT-P13 was as good as infliximab in controlling pain in adult patients ages 18-75 years old with rheumatoid arthritis.

Yoo, Racewicz , Brzezicki, et al. separated patients with 1:1 ratio giving half CT-P13 and half infliximab and measured their mean change in pain over 54 weeks.[6] Jørgensen performed a crossover, taking patients who had been on infliximab for at least 6 months and switching half of them to start CT-P13 while leaving the other half to remain on infliximab.[9] Yoo, Prodanovic, Jaworski, et al. did a crossover study using the patients from the initial phase III clinical trial who had completed the 54 weeks of treatment. They continued the CT-P13 patients on their CT-P13 regimen and switched the patients who were on infliximab to CT-P13.[10] Each of these studies measured the patients' improvement by monitoring their change in pain from baseline either by VAS or DAS28.[10]

The Yoo, Racewicz , Brzezicki, et al. study enrolled 606 subjects with active RA that had failed methotrexate treatment alone to receive either CT-P13 or infliximab.[6] Baseline demographics and characteristics were similar between the two groups.[6] Patients received methotrexate and folic acid weekly and 2 hour infusions of either CT-P13 or infliximab at week 0, 2, 6, and then every 8 weeks up to week 54.[6] Patients were premedicated with antihistamines at the discretion of the investigator. [6] The study measured change in VAS score at baseline, week 14, week 30 and week 54 to evaluate the results of the interventions.[6] In this study the mean change of pain between baseline and week 54 +/- SD was -30.2 +/- 28 for CT-P13 and was -28 +/- 26.9 for infliximab.[6] Table 2 has a summary of the results below. The efficacy of this study was decided if the CI of 95% for treatment difference was within +/-15% and it was between 6-10%, effectively showing that the estimate of treatment effect was precise.[6] These results allowed the authors to confidently say the CT-P13 treatment had comparable efficacy to infliximab in treating pain in patients who have RA up to week 54.[6] Adverse events from the study were similar between the two groups.[6]

TABLE 2. VAS results measuring change in pain for Yoo, Racewicz , Brzezicki, et al.[6]

	VAS score for the patient baseline assessment of pain	VAS score for the patient assessment of pain week 54	VAS score for the patient assessment of pain change from baseline	95% CI
CT-P13	65.7+/-17.8	35.0 +/- 21.2	-30.2 +/-23.8	6-10%
infliximab	65.5 +/- 17.7	37.4 +/- 24.7	-28.4 +/- 26.9	

The Jørgensen et al. study enrolled 482 subjects with autoimmune diseases including Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, who had been on infliximab for at least 6 months, and randomly assigned them to either continue treatment with infliximab or switch to CT-P13.[9] Both treatment groups were similar for baseline demographics and disease characteristics.[9] Number of infusions varied depending on treatment regimen between infusions every 4 weeks (14 total infusions) to infusions ever 12 weeks (5 total infusions).[9] The study measured the results of the intervention by looking at the change in the DAS28 score between baseline and 52 weeks.[9] This study combined the DAS28 score for rheumatoid arthritis and psoriatic arthritis.[9] For infliximab, the DAS28 score changed from 2.5 at baseline to 0.3 and for CT-P13 it changed from 2.2 at baseline to 0.1, as seen in table 3 below. The efficacy of this study was decided if the CI of 95% for treatment difference was within 15% and it was between -.07-0.61%, effectively showing that the estimate of treatment effect was precise. The results of this study show that switching from infliximab to CT-P13 was similar to continuing the patient on the infliximab treatment.[9] The rate of adverse events reported in this study was comparable between the two drugs.[9]

TABLE 3. Measuring change in DAS28 score for Jorgensen et al.[9]

	DAS28 score baseline	DAS28 score at 52 weeks	Difference at 52 weeks	95% CI

CT-P13	2.2	0.1	0.27	-.07-0.61%
infliximab	2.5	0.3		

The Yoo, Prodanovic, Jaworski, et al. study was a crossover study from his original study, this time looking at the effects of switching from infliximab to CT-P13. The study enrolled 302 participants that had previously completed the 54 weeks phase III trial, 158 continued CT-P13 and 144 who switched from infliximab to CT-P13.[10] All patients were concomitantly treated with methotrexate and folic acid. [10] Both treatment groups were similar for baseline demographics and disease characteristics. [10] The study looked at the results by measuring a mean decrease in VAS score from baseline, which was prior to the treatment received in the clinical trial, at week 54, now defined as the beginning of this trial, and week 102, end of this trial.[10] The patients who remained on CT-P13 had a mean decrease in VAS from baseline of 32.4 compared to a mean decrease of 35 from baseline with the group who switched from infliximab to CT-P13.[10] The data is shown in table 4 below.[10] The value of this study was determined by the response rates measured with the ACR20.[10]At week 102 there was a 71.7% response rate in the maintenance group and 71.8% response rate for the switch . [10] The efficacy of this study was decided if the CI of 95% for treatment difference was within 15% and it was between -10-10%, effectively showing that the estimate of treatment effect was precise (Table 5).[10] Adverse events that occurred during the extension study were fairly similar between the maintenance group and the switch group.[10]

TABLE 4. VAS results measuring change in pain for Yoo, Prodanovic, Jaworski, et al. [10]

	VAS score for the patient baseline assessment of pain	VAS score for the patient assessment of pain change from baseline at week 54	VAS score for the patient assessment of pain change from baseline at week 102	Mean decrease in VAS between week 54 and week 102

Pt staying on CT-P13 (maintenance group)	63.8	-31.3	-32.4	-1.1
Pt switching from infliximab to CT=P13 (switch group)	65.8	-32.4	-35	-2.6

TABLE 5. Measuring response rate in ACR20 score for Yoo, Prodanovic, Jaworski, et al [10]

	ACR20 response rate at week 102	95% CI
Pt staying on CT-P13 (maintenance group)	71.7%	-10-10%
Pt switching from infliximab to CT=P13 (switch group)	71.8%	

Infliximab and its biosimilar CT-P13 are tumor necrosis factor inhibitors.[6] By way of their mechanism of action and as seen in the studies above the most common side effects were infections. The infections ranged from latent tuberculosis (TB), upper respiratory tract infections (URTI), urinary tract infections (UTI), lower respiratory tract infections (LRTI), flare in RA activity, and herpes virus infection.[6, 9, 10] Other common adverse reactions were infusion reactions, elevated LFTs, headaches, and abdominal pain but they were similar between the two drugs. [6, 9, 10] The amount of adverse reactions reported in the studies was marginal and there was limited for safety with use of either CT-P13 or infliximab.

DISCUSSION

Infliximab is a biologic commonly used to treat rheumatoid arthritis refractive to prior treatment with DMARDs.[3] As discussed above, infliximab has become increasingly more expensive. Fortunately, its patent has recently ended, allowing for the creation of biosimilars such as CT-P13. CT-P13 was FDA approved for use in the United States in 2016 and goes by the brand name Inflectra.[13] It is contraindicated to use CT-P13 >5mg/kg in patients with moderate to

severe heart failure and in patients who are allergic to infliximab, have known history of allergies to inactive components of CT-P13 or to any murine proteins.[13] CT-P13 has a black box warning for 1) increased risk of serious infections leading to hospitalizations or death, 2) lymphoma and other malignancies some fatal have been noted in children and adolescents treated with tumor necrosis factor blockers, and 3) hepatosplenic T cell lymphoma has been noted in patients who almost all had been concomitantly treated with azathioprine or 6 mercaptopurine at or prior to diagnosis.[13] CT-P13 is FDA approved for use in adult and pediatric crohn's, adult ulcerative colitis, rheumatoid arthritis in combination with methotrexate, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Currently the FDA does not allow biosimilars to be substituted for the biologics at the pharmacy level.[14] Practitioners must specifically prescribe the biosimilar.[15] Rheumatoid arthritis is a lifelong disease and patients can be on biologics for years. A limitation in the studies was the high losses to follow up of 25% in Yoo DH, Racewicz A, Brzezicki J, et al. and 13% in Yoo DH, Prodanovic N, Jaworski J, et al. Another limitation was Jørgensen et al did not do an intent to treat analysis. Having high losses to follow up and no doing an intent to treat analysis can decrease the validity of these studies. Another limitation was length of follow up. Throughout the studies it was shown that CT-P13 had the same efficacy as infliximab when treating pain in patients with RA, but the studies stopped at either one or two years. There was no long term follow up to see if the efficacy remains the same or if there is an increased risk for immunogenicity the longer someone is on the medication.

CONCLUSION

Yoo DH, Racewicz A, Brzezicki J, et al. and Yoo DH, Prodanovic N, Jaworski J, et al. randomized control trial and his crossover study showed that CT-P13 was as effective as infliximab in controlling pain in adult patients between 18-75 years old with RA. The studies

showed that pain control was comparable, and risk of adverse reactions were similar when comparing treatment with CT-P13 and infliximab. The Jørgensen study looked at multiple autoimmune diseases, not specifically RA, which may have led to a greater influence on the results being favorable for the RA patients. Further research can be done to see if premedicating all patients with antihistamines prior to infusions decrease infusion reactions. Further crossover studies should be done between the two biologics to further evaluate efficacy, and safety (including risk of development of immunogenicity). Doing further research to explore the limitations of the prior studies will help solidify the results and instill confidence in the practitioners' judgment to alter traditional treatment methods for maximum patient benefit.

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